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Pulmonary Interstitial Disease Mimicking Idiopathic Pneumonia Syndrome as the Initial Site of Relapse of Neuroblastoma Following Autologous Bone-Marrow Transplantation: A Case Report

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Pulmonary interstitial infiltrates are a common diagnostic dilemma following bone-marrow transplantation. We present a case report of a child presenting with recurrent, metastatic neuroblastoma after bone-marrow transplantation, manifested initially as pulmonary interstitial disease mimicking idiopathic pneumonia syndrome. © 1996 Wiley-Liss, Inc.

Key words: neuroblastoma, relapse location, idiopathic pneumonia syndrome, open lung biopsy, autologous bone-marrow transplantation

INTRODUCTION

Metastatic childhood neuroblastoma remains a significant therapeutic challenge. In contrast to many other childhood malignancies, the long-term survival of children with disseminated neuroblastoma remains dismal [1,2]. Due to the grave prognosis of this common pediatric solid tumor, several cooperative groups are studying the effects of dose intensification, aggressive surgery, and autologous bone-marrow transplantation for these patients [3,4]. It remains uncertain whether or not treatment intensification results in improved long-term cures [5]. However, treatment intensification does lead to increased toxicity and perhaps the emergence of more unusual sites of initial relapse of neuroblastoma, including the central nervous system [6,7].

A common site of toxicity following bone-marrow transplantation is the lung [8]. Diseases affecting the lung include opportunistic bacterial, viral, and protozoal pathogens, therapy-related toxicity, and the ill-defined entity known as idiopathic pneumonia syndrome or pulmonary interstitial pneumonitis [9]. Often, diagnosis of pulmonary infiltrates after bone-marrow transplantation or intensive chemoradiotherapy represents a clinical challenge and requires open-lung biopsy for pathologic diagnosis.

This case report describes a child with pulmonary decompensation and interstitial pneumonitis 3 months following autologous bone-marrow transplantation for neuroblastoma. Open-lung biopsy revealed recurrent neuroblastoma as the etiology of the pulmonary infiltrate and as the initial site of disease relapse.

CASE REPORT

M.H. is a 6-year-old boy diagnosed at the University of Alabama at Birmingham in March 1994 with metastatic neuroblastoma. The initial clinical presentation was bone pain and anemia. A primary tumor was identified in the right adrenal gland with metastasis to lymph nodes, liver, bone parenchyma, and bone marrow. Diagnosis was based on the finding of characteristic tumor clumps in bone marrow specimens, the adrenal primary tumor, and elevated urinary catecholamines (homovanillic acid (HVA), 171 μg/mg creatinine (normal, <14); vanillymandelic acid, 11 μg/mg creatinine (normal, <8). The tumor was staged as Pediatric Oncology Group (POG) stage D (International Neuroblastoma Staging System stage IV) [10].

The patient was treated on a POG therapeutic protocol

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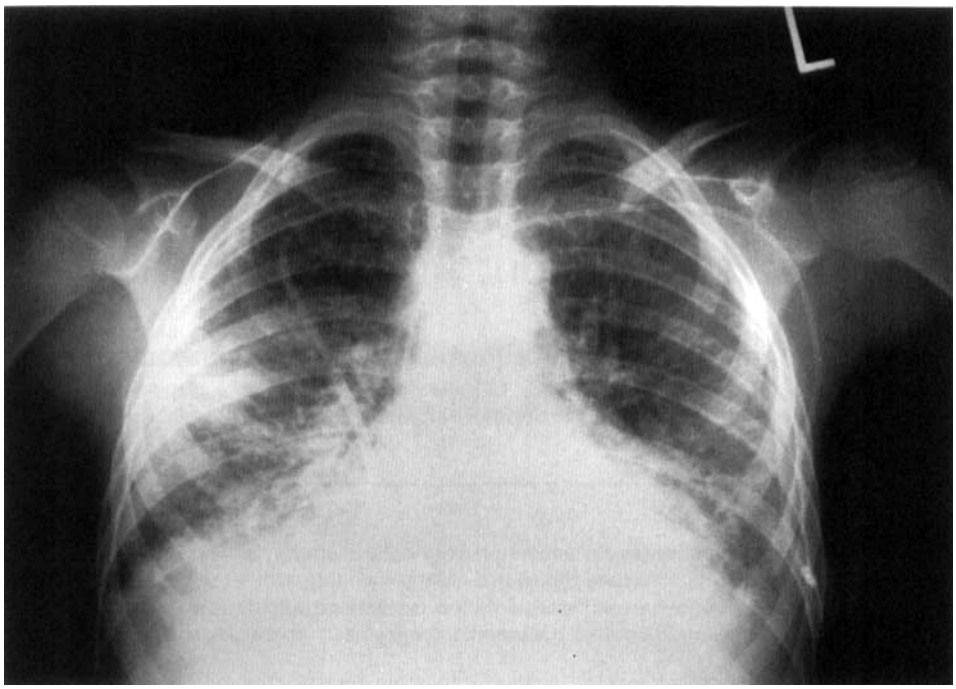

Fig. 1. Chest radiograph at presentation. Radiograph from date of admission. Note diffuse interstitial infiltrates throughout both lungs.

(9340/9341/9342) consisting of an upfront phase II window in which the patient received taxol, followed by combination alternating chemotherapy regimens which included cisplatin, etoposide, cyclophosphamide, doxorubicin, vincristine, carboplatin, and ifosfamide. Following an excellent response to adjuvant chemotherapy, a second-look surgery was performed for primary tumor resection, followed by local radiation to the primary tumor bed for control of microscopic residual disease prior to planned purged, autologous bone-marrow transplantation. Bone-marrow transplantation was performed with an etoposide, carboplatin, and cyclophosphamide preparation at Duke University Medical Center in October 1994. The infused marrow was documented free of tumor cells, utilizing immunocytologic methods. The marrow was purged prior to reinfusion by immunomagnetic bead purging techniques, as previously described [11]. The transplant procedure was well-tolerated, and the patient returned to Birmingham in December 1994. A complete posttransplantation staging workup was completed in mid-December, consisting of computerized tomography scans of the chest, abdomen, and pelvis, bone scan, bone-marrow aspiration, and biopsy with tumor assessment by morphologic evaluation and urinary catecholamines (HVA, 14 μg/mg creatinine; VMA, 12 μg/mg creatinine). No evidence of persistent or recurrent neuroblastoma was identified.

In early January 1995, the patient presented with onset of fever (101.6°F), shoulder and chest pain, respiratory distress, and hypoxemia (oxygen saturation, 87% on room air). Physical examination was significant only for tachypnea with clear lung fields, cyanosis, and labored respirations. Screening laboratory studies were unremarkable, including stable complete blood count. Chest radiography revealed bilateral pulmonary interstitial densities (Fig. 1). The patient was treated with broad-spectrum antibiotics including intravenous trimethoprim/sulfamethoxazole, nafcillin and ceftazidime, oxygen, and supportive care. On the day following admission a bronchoalveolar lavage was performed to evaluate for *Pneumocystis carinii* infection and demonstrated only the presence of alveolar macrophages and occasional polymorphonuclear leukocytes. Silver stain failed to demonstrate any *Pneumocystis carinii.* Based on the nondiagnostic bronchoalveolar lavage and the presence of worsening respiratory distress, an open-lung biopsy of the lingula was performed the following day.

The open-lung biopsy specimen revealed metastatic neuroblastoma as the etiology of the interstitial pulmonary densities (Fig. 2). Radiographic reevaluation and staging following return of the biopsy results demonstrated neuroblastoma in the bone marrow. Urinary catecholamines were marginally elevated (HVA, 34 μg/mg creatinine; VMA, 17 μg/mg creatinine). Further chemotherapy was declined by the family, the child's respiratory status continued to deteriorate, and he died of respiratory failure 3 days later.

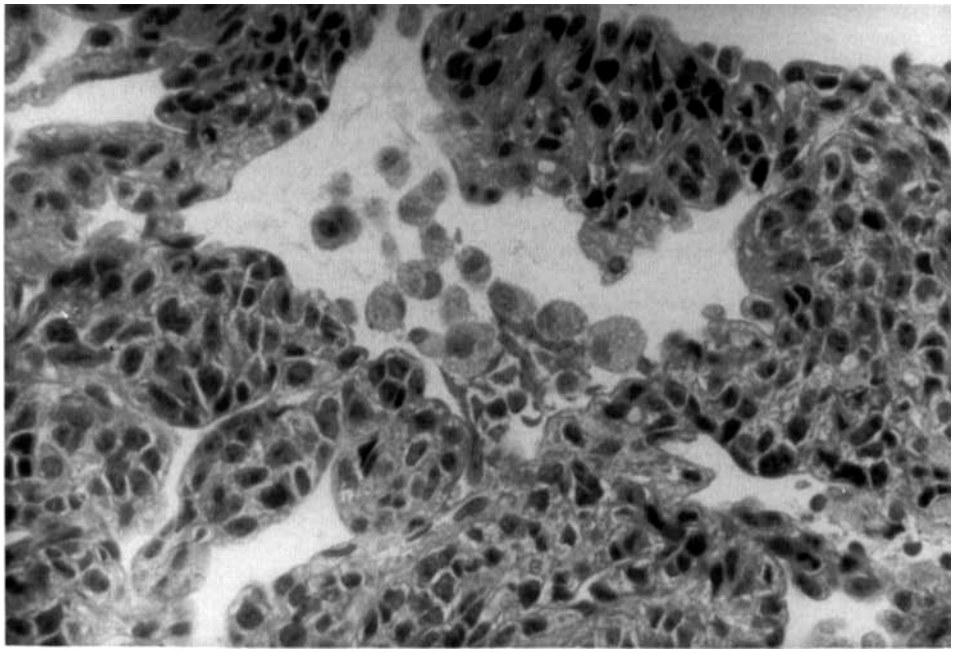

Fig. 2. Open-lung biopsy. A portion of pulmonary parenchyma that is diffusely involved by metastatic small blue-cell tumor (neuroblastoma) (hematoxylin and eosin, original magnification ×400).

DISCUSSION

Interstitial pulmonary infiltrates present diagnostic dilemmas in patients undergoing multiagent chemotherapy, radiotherapy, or bone-marrow transplantation for malignant diseases. The broad differential diagnosis of such infiltrates includes infections, drug- or radiation-induced pulmonary damage, damage from acute or chronic graft vs. host disease, disease infiltration, or the entity of idiopathic pneumonia syndrome [8,9,12]. Usually the clinical presentation of fever, tachypnea, hypoxemia, and bilateral interstitial pattern on chest radiograph suggests an opportunistic infection with *Pneumocystis carinii* pneumonia or idiopathic pneumonia. In the case presented above, other etiologies seemed unlikely due to the lack of radiation to the lungs or use of chemotherapeutic agents known to result in pulmonary fibrosis, and the lack of other evidence of graft vs. host disease in this autologous marrow-transplant recipient.

Relapse of neuroblastoma likewise appeared unlikely due to the recent (3 weeks previously) negative complete staging workup and lack of other symptoms. Neuroblastoma can and does metastasize to the lungs, usually as end-stage disease, and usually in a parenchymal or miliary pattern [1,2,13]. Rarely if ever is pulmonary interstitial involvement the sole site of initial recurrence. Despite these assumptions and probabilities, the symptoms in the patient reported were solely the consequence of recurrent metastatic neuroblastoma. Following documentation of recurrent disease, bone-marrow investigation revealed neuroblastoma metastatic to the marrow. However, the marrow disease was asymptomatic from the standpoint of count modification until the pulmonary disease was defined.

It remains unclear whether bone-marrow transplantation offers a curative advantage in disseminated neuroblastoma [5]. Clearly, however, transplantation may result in prolonged survival in some patients. With longer survival and newer aggressive therapeutic interventions, patterns of relapse of neuroblastoma may change. Clinicians must be diligent in the evaluation of patients with neuroblastoma and remember the tenacity of the disease when confronted with clinical dilemmas. The importance of diagnostic studies of pulmonary infiltrates, including bronchoalveolar lavage and open biopsy in immunocompromised patients, is well-defined. The case reported here reinforces the importance of tissue diagnosis and defines the pulmonary interstitium as a possible site of initial relapse in neuroblastoma.

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